

FC-95, FC-143 and FM-3422 - 90 Day Subacute Toxicity Studies

Conducted at IRDC - Review of Final Reports and Summary

OVERALL SUMMARY AND RECOMMENDATIONS

FC-95 was the most toxic of the three compounds studied and certainly more toxic than anticipated. It produced mortalities in rats at a dietary dose of 100 ppm ( $\approx 10$  mg/kg/day) and in monkeys at an oral dose of 4.5 mg/kg/day. The primary target organs in rats were the liver, hematopoietic tissues and upper gastrointestinal tract and in monkeys, the gastrointestinal tract although no pathological lesions were reported. FC-143 appeared to be the least toxic of the three compounds studied and produced no mortalities in rats at dietary doses as high as 1000 ppm ( $\approx 100$  mg/kg/day). However, definite evidence of liver toxicity was seen at the high dose. In monkeys, FC-143 caused deaths at oral doses of 100 (4/4) and 30 (3/4) mg/kg/day and evidence of effects on hematopoietic tissue at these lethal doses. Like FC-95 and FM-3422, FC-143 also produced clinical evidence of gastrointestinal toxicity but no associated pathological lesions. FM-3422 caused deaths in rats at dietary doses of 1000, 3000 and 10,000 ppm ( $\approx 100$ , 300 and 1000 mg/kg/day respectively) and in monkeys (1/4) at an oral dose of 30 mg/kg/day. The primary target organ in rats appeared to be the liver although there was some gross evidence of kidney and upper gastrointestinal tract involvement as well. In monkeys, the gastrointestinal tract was affected clinically, but there were no pathological lesions reported at necropsy.

The goals of conducting these 90 day subacute toxicity studies of 1) defining doses for chronic experiments and 2) obtaining general toxicological information on the three compounds appear to have been met. However, several questions surfaced that deserve further clarification. The apparent effect of FC-95 on the liver and hematopoietic system of rats should be studied for reversibility. The question of clinical gastrointestinal signs in monkeys with all three compounds without any gross or microscopic pathology is certainly perplexing, but may not be worth further pursuit since the oral route is not a likely one for man. If another study with FC-143 is conducted to help define the gastrointestinal and hematopoietic effects, the dog should be considered. Since the most likely route of exposure in plant workers is by inhalation, an inhalation study, probably with FM-3422, could be useful in evaluating any effects via pulmonary exposure. Marv Case and Bill McCormick are preparing protocols for follow-up to the toxicity questions mentioned.

Because of the apparent persistence of these fluorochemicals in the body, the most important question remains possible long term effects. Although lifetime rodent studies have limitations in predicting chronic effects (carcinogenesis) for man, they are still considered the most reliable indicators available. Unless there are adequate data through human epidemiological evaluations that can reasonably assure relative safety of these compounds following long term exposure, lifetime rodent studies should be undertaken as soon as possible. It may be possible to limit the number of compounds evaluated in lifetime rodent studies to one or two if metabolic data can be used to establish a common linkage between compounds.

**Exhibit  
1199**

State of Minnesota v. 3M Co.,  
Court File No. 27-CV-10-28862

3MA00593073

INDIVIDUAL SUMMARIES

FC-95

Study No. 137-085 - 90 Day Subacute Rat Toxicity Study

Dietary levels of FC-95 were administered to five male and five female rats/level at 30, 100, 300, 1000 and 3000 ppm which approximates 3, 10, 30, 100 and 300 mg/kg/day respectively. All rats at the three highest doses and 5/10 at 100 ppm died during the study. Predominant signs observed included emaciation, convulsions, altered posture, ocular, oral and anal discharges, hyperreactivity and reduced motor activity. Mortalities occurred in a sequence related to dose, with earlier deaths seen at the highest level. There was compound and dose related evidence of reduced body weight gain and food consumption with actual weight loss at higher lethal doses. At 30 ppm only slight body weight effects were present. The most notable clinical pathology effects were observed at 100 ppm (values not obtained at higher levels) and consisted of enzyme level increases suggestive of possible liver toxicity and decreased erythrocytic values (principally hemoglobin and hematocrit with slight lowering of red cell counts) indicating an anemia. Pathologically, the most consistent and apparent compound related effect involved liver, hematopoietic tissues (thymus, bone marrow, spleen, mesenteric lymph nodes), gastrointestinal tract, muscle and skin.

In summary, FC-95 was relatively toxic to rats causing mortalities at dietary doses as low as 100 ppm ( $\approx$  10 mg/kg/day). Primary target organs appeared to be liver, hematopoietic tissues, stomach and small intestine with some indication of a compound related effect in muscle and skin.

Study No. 137-087 - 90 Day Subacute Rhesus Monkey Toxicity Study

FC-95 was administered by gastric intubation as an aqueous suspension to two male and two female rhesus monkeys/level at doses of 10, 30, 100 and 300 mg/kg/day for up to 20 days. Because of unexpected early mortalities in all monkeys at all levels (days 2-4 at 300, 3-5 at 100, 7-10 at 30 and 11-20 at 10 mg/kg/day), the study was inconclusive. Prominent signs observed consisted of anorexia, decreased activity, emesis with some diarrhea, body stiffening, general body trembling and twitching, weakness, convulsions and prostration. No clinical pathology work was done because of the short study duration. The only pathological lesions reported consisted of gross yellowish-brown liver coloration at 100 and 300 mg/kg/day but no histopathologic basis for this finding was observed.

In summary, FC-95 proved to be considerably more toxic to monkeys than anticipated resulting in early deaths preceded by gastrointestinal and central nervous system signs. Although far from definitive, this study suggested the gastrointestinal tract and possibly liver as target organs.

Study No. 137-092 - 90 Day Subacute Rhesus Monkey Toxicity Study (Second Study)

Since all monkeys died in the first FC-95 study (137-087), a second experiment was conducted using oral gavage doses of 0.5, 1.5 and 4.5 mg/kg/day administered to two male and two female monkeys/dose. The controls were the same monkeys used in the first FC-95 experiment. All 4.5 mg/kg monkeys exhibited signs of gastrointestinal tract toxicity (anorexia, emesis, black stools, dehydration) starting on day 1 or 2 of the study, and all died or were sacrificed in extremis between weeks 5-7. Prior to death, these monkeys showed marked or severe rigidity, convulsions, general body tremors, prostration and loss of body weight. The monkeys at lower doses all survived, but evidence of gastrointestinal toxicity was observed both at 1.5 and 0.5 mg/kg/day. The only consistent clinical pathology observation reported was decreased alkaline phosphatase values at all three doses. No gross pathological lesions considered compound related were observed and the only microscopic pathology of apparent compound relationship consisted of lipid depletion in the adrenals, atrophy of pancreatic exocrine cells and atrophy of the serous alveolar cells of the submandibular salivary glands in high dose monkeys. These latter effects may be due to general debilitation of the animals.

In summary, FC-95 was relatively toxic to rhesus monkeys producing deaths at doses as low as 4.5 mg/kg/day in 5-7 weeks. The apparent target organ was the upper gastrointestinal tract although no pathological lesions were reported even at the high dose.

FC-143

Study No. 137-089 - 90 Day Subacute Rat Toxicity Study

Dietary levels of FC-143 administered to five male and five female rats/level were 10, 30, 100, 300 and 1000 ppm which approximates 1, 3, 10, 30 and 100 mg/kg/day respectively. Clinically, the only effect observed was slightly decreased body weight gains at 300 and 1000 ppm. Clinical pathology abnormalities reported in high dose male rats only included slightly lowered erythrocyte counts, and elevated BUN and alkaline phosphatase values. There were several other variations from control groups in the clinical pathology parameters including fairly consistent lowering of calcium levels at all doses, but these were not considered abnormal based on the contract laboratory's comparison to background control data. Pathological abnormalities were confined to the liver and included gross enlargement and discoloration at 1000 ppm, increased organ weights at 1000 and 300 ppm and several microscopic changes at 1000 ppm.

In summary, FC-143 was well tolerated in rats at doses up to and including 300 ppm ( $\approx$  30 mg/kg/day). There was obvious liver toxicity at 1000 ppm ( $\approx$  100 mg/kg/day), but no mortalities occurred.

Study No. 137-090 - 90 Day Subacute Rhesus Monkey Toxicity Study

FC-143, suspended in 0.5% methocel, was administered by gastric intubation to two male and two female rhesus monkeys/dose at 3, 10, 30 and 100 mg/kg/day. All high dose monkeys died during weeks 2-5 and 3/4 30 mg/kg monkeys died during the last half of the study. All monkeys that died showed clinical evidence of gastrointestinal toxicity (anorexia, emesis, dark stools), but there were no associated pathological lesions found at necropsy. No mortalities occurred and only occasional signs of gastrointestinal effects were reported at the two lower doses except for one 10 mg/kg monkey that had signs of gastrointestinal toxicity for several days late in the study. There were a few abnormalities reported in clinical pathology parameters, but no consistent pattern was observed. Gross and microscopic pathological lesions were restricted to the two highest dose levels and consisted of lipid depletion in adrenals, hypocellularity of bone marrow and atrophy of lymphoid follicles of the spleen and lymph nodes.

In summary, FC-143 was less toxic than FC-95 in rhesus monkeys but, at lethal doses (100 and 30 mg/kg/day), evidence of effects on hematopoietic tissue was seen. Like FC-95, the gastrointestinal tract also appeared to be a target organ although this was not confirmed on histopathological examination.

FM-3422

Study No. 137-086 - 90 Day Subacute Rat Toxicity Study

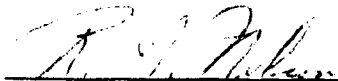
FM-3422 was administered in the diet to five male and five female rats/level at 30, 100, 300, 1000, 3000 and 10,000 ppm which corresponds to approximately 3, 10, 30, 100, 300 and 1000 mg/kg/day respectively. All rats at the 1000, 3000 and 10,000 ppm levels died between days 9 and 29. Prominent signs observed in these rats included emaciation, altered posture, convulsions, reduced motor activity and/or increased sensitivity. At 30 ppm, a slight decrease in body weight gain in females was the only clinical effect reported. There were also some slight abnormalities in serum enzyme levels, but no pronounced trends. Likewise, minimal effects were seen at 100 ppm. At 300 ppm there appeared to be increased compound related clinical signs, decreased body weight gain and food consumption, depressed hematological parameters and several alterations in clinical chemistry values. Pathologically, the liver was grossly enlarged with accentuated lobulation and discoloration with the 300 ppm group being more severely effected than the 1000 or 3000 ppm rats. This apparent reversed order of toxicity related to dose could be due to the early mortalities of the high dose rats and, therefore, a short dosing duration. The liver abnormalities seen grossly were associated with increased liver weights and microscopic lesions. Some kidney discoloration and evidence of stomach irritation were also observed grossly at 300 ppm.

In summary, FM-3422 was lethal at doses of 1000, 3000 and 10,000 ppm which is approximately 100, 300 and 1000 mg/kg/day respectively. The liver appeared to be the primary target organ, but there was gross pathological evidence of possible kidney and stomach involvement at the 300 ppm level also.

Study 137-088 - 90 Day Subacute Rhesus Monkey Toxicity Study

FM-3422, suspended in propylene glycol, was administered by gavage to two male and two female monkeys/level using doses of 1, 3, 10 or 30 mg/kg/day. The vehicle appeared to cause anorexia early in the study necessitating volume reduction from 5 to 2 ml/kg. The only mortality occurred in one high dose monkey the last week of dosing. Gastrointestinal signs consisting of emesis, diarrhea and black stools with mucus or bloody mucus were seen in most monkeys from most groups. There were no clinical pathology observations that appeared to be significant compound effects. Pathological lesions reported included lipid depletion of adrenals and atrophy of pancreatic exocrine glands at 30 mg/kg only.

In summary, FM-3422 caused mortality at 30 mg/kg in 1/4 monkeys and appeared to primarily effect the gastrointestinal tract although there was no supporting microscopic evidence.

  
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Date 3/20/79

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